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Selenium-Containing Heterocycles From Isoselenocyanates: Synthesis of Ethyl 4-Oxo-2-amino-4,5-dihydroselenophene-3-carboxylates

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Abstract: Aryl and alkyl isoselenocyanates **2** react with ethyl γ-chloroacetoacetate (**1**) in the presence of triethylamine to give the corresponding 4-oxo-2-amino-4,5-dihydroselenophene-3-carboxylates **4a-f** in moderate to good yields.

Key Words: Selenium heterocycles, Isoselenocyanates, Selenophenes, Cyclization, *β*-Ketoester, Crystal structure

INTRODUCTION

Selenium containing heterocycles are of increasing interest because of the antitumor, antibacterial and other biological activities of some representatives [1]. During our efforts devoted to the chemistry of selenaheterocycles, we also became interested in the synthesis of selenophenes. There are many articles and reviews dealing with the preparation of selenophenes [2], however, to the best of our knowledge, no synthesis starting from isoselenocyanates has been published. On the other hand, several procedures concerning the preparation of thiophenes by using isothiocyanates have been described [3]. For example, syntheses of some 4-oxothiophenes have been reported by Faull and Hull [4] as well as by Ibrahim, Sadek, Aziz, and Elnagdi [5] in the 80's. Compounds of this type, including 4-oxofurans, are known as novel antiallergic agents [6].

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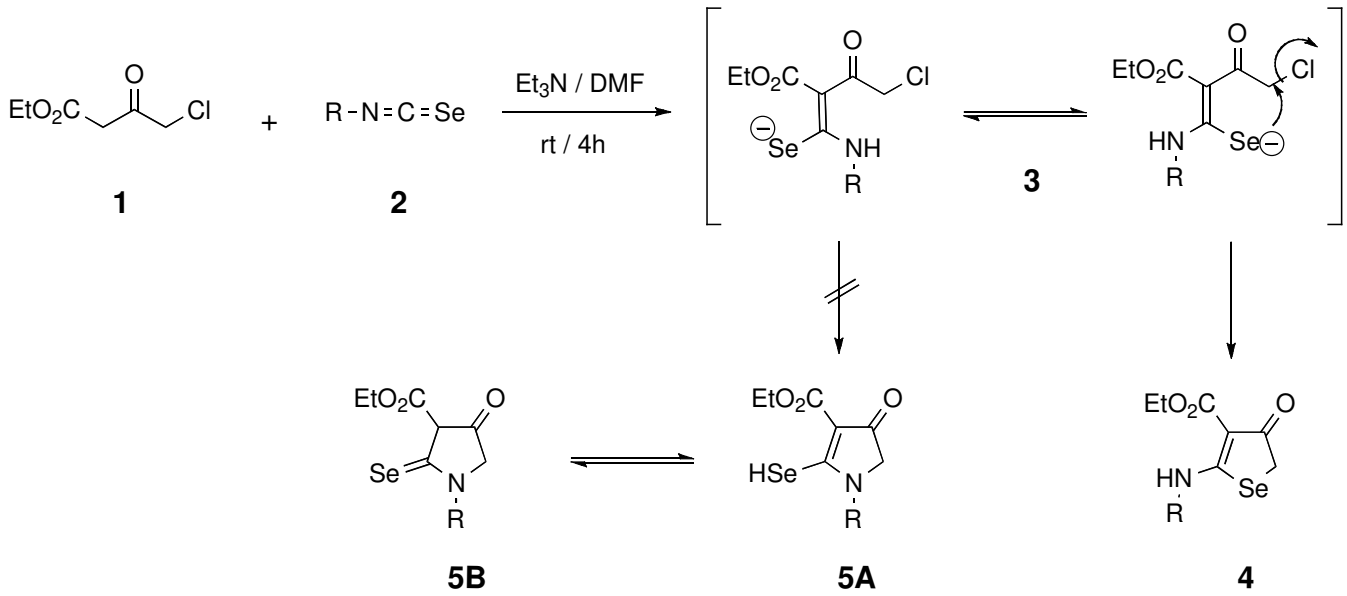
As a part of our program aimed at the development of simple procedures for the preparation of selenium-containing heterocycles [7-14], we have recently reported on the utility of isoselenocyanates for the synthesis of selenazetidines [15], selenazolidines [16,17], selenazines [16,18], selenadiazines [19], selenazepines [20], selenorhodanines [21], and triazoleselones [22]. As a continuation of this work, we report here on a novel and efficient synthesis of selenophene derivatives.

It was expected that the carbanion generated from ethyl γ-chloroacetoacetate (**1**) and triethylamine in DMF reacts with aromatic and aliphatic isoselenocyanates **2** to give intermediate keten-N,Se-acetals of type **3**. The latter, in an intramolecular nucleophilic substitution, can cyclize to give the selenophene ring system **4** (*Scheme 1*). Alternatively, ring closure via nucleophilic substitution by the N-atom could lead to pyrrolidine derivatives of type **5**. Analogous ring closure reactions, which gave azoleselones, have been described earlier [21,22]. The necessary isoselenocyanates **2** can be prepared easily from the corresponding *N*-arylformamides by treatment with phosgene and elemental selenium by following a slightly modified Barton procedure [23].



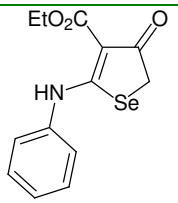
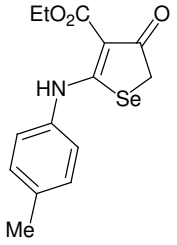
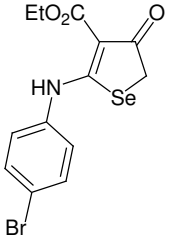
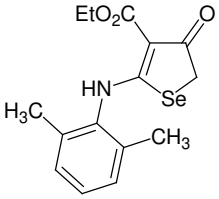
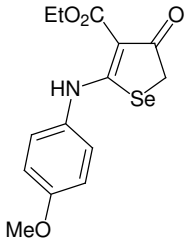
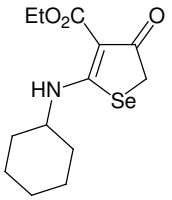
Scheme 1

RESULTS AND DISCUSSION

After stirring an equimolar mixture of ethyl γ-chloroacetoacetate (**1**), the respective isoselenocyanate **2**, and triethylamine in DMF at room temperature for four hours, the solvent was

evaporated. Column chromatography of the solid residue on silica gel with hexane/ethyl acetate and recrystallization of the major product from ethyl acetate gave ethyl 2-amino-4,5-dihydro-4-oxoselenophene-3-carboxylates **4** in fair yields (Table 1).

Table 1: Preparation of Selenophenes 4 from Isoselenocyanates 2

Entry	Selenophenones **4**	M.p. (°C)	Yield (%)
a		152–154	52
b		151–153	56
c		186–188	54
d		163–165	26
e		169–171	51
f		Oil	44

The structures of the products were established on the basis of their spectroscopic data and elemental analyses. Indicative are the IR absorptions at ca. 1660 and 1640 cm^{-1} for the keto and ester C=O groups, respectively. In the mass spectra (CI mode), the respective $[M+1]^+$ peak appears as the base peak (100%), and the ^1H NMR spectra show the expected signals. Most informative are the ^{13}C NMR spectra with three signals for sp^2-C atoms at ca. 193, 182, and 167 ppm for C(4)=O, C(2), and CO_2Et, respectively. The atom C(3) absorbs at ca. 99 ppm. In the case of **4b**, an X-ray crystal-structure determination was carried out, which confirmed the proposed structure (Fig. 1).

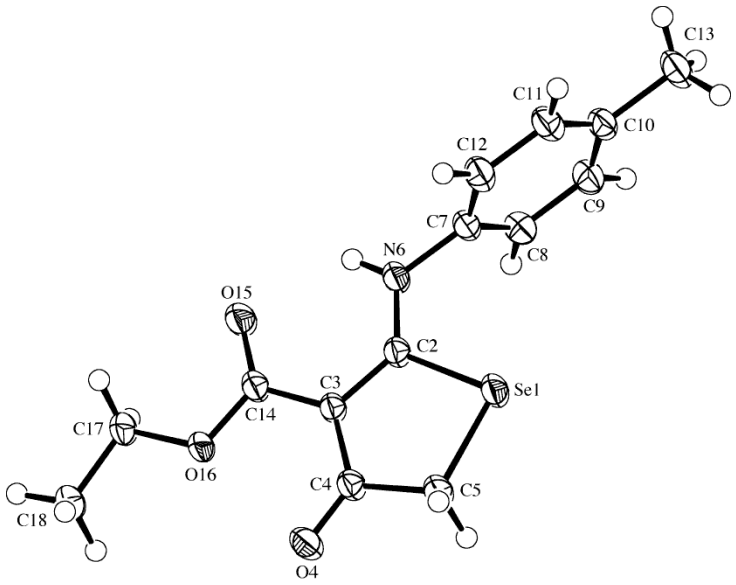


Fig. (1). ORTEP plot [24] of the molecular structure of **4b** (50% probability ellipsoids; arbitrary numbering of atoms)

In the crystal structure of **4b** all atoms of the molecule, except for the atoms of the 4-methylphenyl ring, form a planar system. When calculated using all atoms except C(8) to C(13), the maximum deviation from the plane is 0.054(2) Å for C(17). The plane of the 4-methylphenyl ring lies perpendicular to the heterocyclic ring plane [angle: 88.94(7)°)]. The amine group HN(6) forms bifurcated hydrogen bonds. One interaction is intramolecular with the ester carbonyl O(15) atom, while the second interaction is intermolecular with the same O-atom of a neighboring molecule, thereby linking pairs of molecules about a centre of inversion into dimeric moieties. The intramolecular interaction forms a closed loop with the graph set motif [25] of S(6), while the intermolecular interaction

creates a loop with the graph set motif of $R^2_{,2}(12)$. Taking both interactions together generates a four-membered loop with a binary graph set motif of $R^2_{,2}(4)$.

In summary, we have evidenced that ethyl γ-chloroacetoacetate (**1**) is a very good precursor of selenophenes **4**. The base-catalyzed reaction with isoselenocyanates **2** proceeds *via* addition of the carbanion of **1** onto the isoselenocyanate to yield the acyclic intermediate **3**, which then undergoes a cyclization via the selenium atom to give **4** via elimination of HCl. The alternative ring closure via nucleophilic attack of the nitrogen atom of **3** (cf. [21,22]), which would lead to a pyrrole derivative, was not observed as a result of the higher nucleophilicity of the selenium atom. Thus, the selenophenes **4** have been easily prepared in a one-pot procedure starting from aryl and cyclohexyl isoselenocyanates. These building blocks are less toxic, relatively stable, safe and easy to handle, and can be synthesized conveniently.

EXPERIMENTAL

General

TLC: silica gel 60 F_{254} plates (0.25 mm; Merck). Column chromatography (CC): silica gel 60 (0.040-0.063 mm; Merck). Melting Points: Büchi B-540 apparatus, in capillaries; uncorrected. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.5 MHz) spectra: Bruker ARX-300 instrument in $CDCl_3$; chemical shifts in ppm. CI-MS: Finnigan SSQ-700 or MAT-90 instrument; NH_3 as carrier gas.

Starting materials

Malononitrile and all halogenated compounds are commercially available (Fluka). Isoselenocyanates were prepared according to Barton's procedure [23] by starting from formamides. Formanilide and *N*-cyclohexylformamide are commercial products (Fluka and Aldrich), *N*-(4-methylphenyl)-, *N*-(4-bromophenyl)-, *N*-(2,6-dimethylphenyl)- and *N*-(4-methoxyphenyl)formamide were prepared from the respective aniline and 95% formic acid [26]. The solution was heated to reflux for 30 min and evaporated to dryness in vacuo. The residue was dissolved in ether and washed with diluted acetic acid (5%), water, and aqueous $NaHCO_3$ (5% aq.). The aqueous layer was extracted with ether, the combined organic extracts were dried with magnesium sulphate and evaporated under reduced pressure. The crude products were purified by recrystallization in EtOH/water.

General Procedure for the Preparation of 4,5-Dihydroselenophene-3-carboxylates 4a-f

A 25 mL round-bottom flask equipped with magnetic stirrer and condenser was charged with a solution of ethyl γ-chloroacetoacetate (**1**, 0.14 mL, 1.03 mmol) in DMF (20 mL). Triethylamine (0.14 mL, 1.03 mmol) was added and the mixture was stirred for 45 min at room temperature. Isoselenocyanate (**2**, 1.03 mmol) was added and the mixture was stirred for 4 h at room temperature before being evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel without any further treatments by using hexane/ethyl acetate (100/0 to 50/50) as the eluant and crystallized from ethyl acetate.

Ethyl 4,5-dihydro-4-oxo-2-(phenylamino)selenophene-3-carboxylate (4a)

Yield: 52%. White crystals. M.p. 152-154°C. IR (KBr): 3441*w br*, 3052*w*, 2983*w*, 1645*s*, 1588*w*, 1550*s*, 1498*w*, 1471*w*, 1410*m*, 1381*m*, 1351*w*, 1282*w*, 1219*m*, 1036*m*, 946*w*, 780*w*, 736*w*. ^{1}H NMR ($CDCl_3$): 1.65 (t, J=7.1 Hz, 3H, CH_3); 3.96 (s, 2H, CH_2); 4.61 (q, J=7.1 Hz, 2H, CH_2O); 7.62-7.73 (m, 5H, arom. CH). ^{13}C NMR ($CDCl_3$): 14.3 (CH_3); 32.6 (CH_2); 60.4 (CH_2O); 99.8 (C(3)); 124.1 (2 arom. CH); 128.0 (1 arom. CH); 129.7 (2 arom. CH); 138.1 (1 arom. C); 167.1 (CO_2); 181.9 (C(2)); 193.2 (CO). CI-MS: 314 (20), 313 (15), 312 (100, $[M+1]^+$), 311 (8, $M^{+\cdot}$), 310 (52), 309 (19), 308 (19). Anal. Calcd for $C_{13}H_{13}NO_3Se$ (311.01): C, 50.33; H, 4.22; N, 4.52. Found: C, 50.43; H, 4.38; N, 4.50.

Ethyl 4,5-dihydro-2-[(4-methylphenyl)amino]-4-oxoselenophene-3-carboxylate (4b)

Yield: 56%. White crystals. M.p. 151-153°C. IR (KBr): 3425*w br*, 3224*w*, 1662*s*, 1636*s*, 1565*s*, 1513*m*, 1470*w*, 1416*m*, 1374*m*, 1224*s*, 1190*w*, 1043*m*, 780*w*. ^{1}H NMR ($CDCl_3$): 1.55 (t, J=7.2 Hz, 3H, CH_3); 2.55 (s, 3H, CH_3); 3.85 (s, 2H, CH_2); 4.52 (q, J=7.1 Hz, 2H, CH_2O); 7.40 (s, 4H, arom. CH). ^{13}C NMR ($CDCl_3$): 14.3 (CH_3); 21.0 (CH_3); 32.6 (CH_2); 60.4 (CH_2O); 99.6 (C(3)); 124.2 (2 arom. CH); 130.2 (2 arom. CH); 135.6 (1 arom. C); 138.2 (1 arom. C); 167.1 (CO_2); 182.2 (C(2)); 193.2 (CO). CI-MS: 328 (18), 327 (9), 326 (100, $[M+1]^+$), 325 (19, $M^{+\cdot}$), 324 (50), 323 (23), 322 (22). Anal. Calcd for $C_{14}H_{15}NO_3Se$ (325.02): C, 51.86; H, 4.66; N, 4.32. Found: C, 51.95; H, 4.83; N, 4.31.

Suitable crystals for the X-ray crystal-structure determination were grown from CH_2Cl_2 by slow evaporation of the solvent.

Ethyl 2-[(4-bromophenyl)amino]-4,5-dihydro-4-oxoselenophene-3-carboxylate (4c)

Yield: 54%. Yellowish crystals. M.p. 186-188°C. IR (KBr): 3442*w br*, 3142*w*, 1658*s*, 1640*s*, 1555*s*, 1529*m*, 1489*w*, 1410*m*, 1377*m*, 1349*w*, 1269*w*, 1217*m*, 1066*w*, 1035*w*, 1011*w*, 782*w*. ^{1}H NMR ($CDCl_3$): 1.33 (t, J=7.2 Hz, 3H, CH_3); 3.65 (s, 2H, CH_2); 4.30 (q, J=7.1 Hz, 2H, CH_2O); 7.19 (d, J=8.2

Hz, 2H, arom. CH); 7.52 (d, J=8.2 Hz, 2H, arom. CH). ^{13}C NMR ($CDCl_3$): 14.3 (CH_3); 32.8 (CH_2); 60.5 (CH_2O); 100.1 (C(3)); 121.6 (1 arom. C); 125.8 (2 arom. CH); 132.9 (2 arom. CH); 137.1 (1 arom. C); 167.2 (CO_2); 182.1 (C(2)); 193.0 (CO). CI-MS: 392 (78), 391 (34), 390 (100, $[M+1]^+$), 389 (23, $M^{+\cdot}$), 388 (47), 387 (19). Anal. Calcd for $C_{13}H_{12}NO_3SeBr$ (388.92): C, 40.13; H, 3.11; N, 3.60. Found: C, 40.31; H, 3.24; N, 3.56.

Ethyl 4,5-dihydro-2-[(2,6-dimethylphenyl)amino]-4-oxoselenophene-3-carboxylate (4d)

Yield: 26%. White crystals. M.p. 163-165°C. IR (KBr): 3441*w br*, 3202*w*, 2979*w*, 1661*s*, 1641*s*, 1593*w*, 1549*s*, 1474*w*, 1404*m*, 1378*w*, 1352*w*, 1273*w*, 1219*m*, 1029*m*, 790*w*. ^{1}H NMR ($CDCl_3$): 1.33 (t, J=7.2 Hz, 3H, CH_3); 2.21 (s, 6H, 2 CH_3); 3.59 (s, 2H, CH_2); 4.28 (q, J=7.1 Hz, 2H, CH_2O); 7.07 (d, J=8.2 Hz, 2H, arom. CH); 7.20 (t, J=8.2 Hz, 1H, arom. CH); 10.98 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): 14.3 (CH_3); 17.8 (2 CH_3); 32.4 (CH_2); 60.2 (CH_2O); 99.0 (C(3)); 128.7 (2 arom. CH); 129.3 (arom. CH); 135.9 (1 arom. C); 136.1 (2 arom. C); 166.9 (CO_2); 185.2 (C(2)); 193.2 (CO). CI-MS: 342 (19), 341 (8), 340 (100, $[M+1]^+$), 339 (21, $M^{+\cdot}$), 338 (54), 337 (19), 336 (19). Anal. Calcd for $C_{13}H_{12}NO_3SeBr$ (339.04): C, 53.26; H, 5.07; N, 4.14. Found: C, 53.20; H, 5.27; N, 3.97.

Ethyl 4,5-dihydro-2-[(4-methoxyphenyl)amino]-4-oxoselenophene-3-carboxylate (4e)

Yield: 51%. White crystals. M.p. 169-171°C. IR (KBr): 3441*w br*, 1638*s*, 1607*w*, 1544*s*, 1511*m*, 1461*w*, 1385*w*, 1336*w*, 1240*w*, 1212*m*, 1183*w*, 1028*m*, 828*w*, 786*w*. ^{1}H NMR ($CDCl_3$): 1.45 (t, J=7.1 Hz, 3H, CH_3); 3.72 (s, 2H, CH_2); 3.89 (s, 3H, CH_3O); 4.41 (q, J=7.1 Hz, 2H, CH_2O); 7.01 (d, J=8.2 Hz, 2H, arom. CH); 7.32 (d, J=8.2 Hz, 2H, arom. CH); 11.54 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): 14.3 (CH_3); 32.6 (CH_2); 55.4 (CH_3O); 60.3 (CH_2O); 99.4 (C(3)); 114.7 (2 arom. CH); 126.2 (2 arom. CH); 130.9 (1 arom. C); 159.3 (1 arom. C); 167.1 (CO_2); 183.0 (C(2)); 193.2 (CO). CI-MS: 344 (8), 343 (33), 342 (100, $[M+1]^+$), 341 (12, $M^{+\cdot}$), 340 (42), 339 (10), 338 (9). Anal. Calcd for $C_{14}H_{15}NO_4Se$ (341.02): C, 49.42; H, 4.44; N, 4.12. Found: C, 49.66; H, 4.62; N, 4.02.

Ethyl 2-cyclohexylamino-4,5-dihydro-4-oxoselenophene-3-carboxylate (4f)

Yield: 44%. Orange oil. IR (film): 3173*w br*, 2933*s*, 2856*m*, 1729*m br*, 1642*s br*, 1561*s*, 1465*m*, 1451*m*, 1408*s*, 1382*m*, 1350*m*, 1304*m*, 1268*m*, 1218*m*, 1149*w*, 1094*w*, 1032*m*, 916*w*, 891*w*, 858*w*, 790*m*, 732*m*. ^{1}H NMR ($CDCl_3$): 1.19-1.47 (m, 7H, CH_3, 2 CH_2); 1.95-1.99 (m, 2H, CH_2); 1.58-1.74 (m, 4H, 2 CH_2); 3.65 (s, 2H, CH_2); 3.26-3.31 (m, 1H, CH); 4.23 (q, J=7.1 Hz, 2H, CH_2O); 10.11 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$)□: 14.3 (CH_3); 24.1 (2 CH_2); 24.9 (CH_2); 32.5 (2 CH_2); 57.5 (CH); 60.0

(CH_2O); 87.0 (C(3)); 157.4 (C(2)); 167.3 (CO_2); 196.5 (CO). CI-MS: 320 (11), 319 (34), 318 (100, $[M+1]^+$), 317 (8, $M^{+\cdot}$), 316 (44), 315 (9), 314 (12). Anal. Calcd for $C_{13}H_{19}NO_3Se$ (317.05): C, 49.37; H, 6.06; N, 4.43. Found: C, 49.46; H, 5.92; N, 4.22.

Crystal-Structure Determination [27]

A crystal of **4b**, obtained from CH_2Cl_2, was mounted on a glass fibre and used for a low-temperature X-ray structure determination. All measurements were made on a *Nonius KappaCCD* area-detector diffractometer [28] using graphite-monochromated MoK_α radiation (λ = 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. Data reduction was performed with *HKL Denzo* and *Scalepack* [29]. The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method [30] was applied. Equivalent reflections were merged. Data collection and refinement parameters are given in [31]. A view of the molecule is shown in *Figure 1*. The structure was solved by direct methods using *SIR92* [32], which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. The amine H-atom was placed in the position indicated by a difference electron density map and its position was allowed to refine together with an isotropic displacement parameter. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Neutral atom scattering factors for non-hydrogen atoms were taken from [33a], and the scattering factors for H-atoms were taken from [34]. Anomalous dispersion effects were included in F_c [35]; the values for f' and f'' were those of [33b]. The values of the mass attenuation coefficients are those of [33c]. All calculations were performed using the *SHELXL97* [36] program.

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[31] Crystallographic data for compound **4b**: Empirical formula: $C_{14}H_{15}NO_3Se$; formula weight: 324.18 g mol^{-1}; crystal color, habit: colorless, prism; crystal dimensions: 0.20 × 0.30 × 0.30 mm; temperature: 160(1) K; crystal system: monoclinic; space group: *C*2/*c*; $Z = 8$; reflections for cell determination: 28982; 2θ range for cell determination: 4 – 60°; unit cell parameters: a = 26.8226(4) Å, b = 7.2506(1) Å, c = 14.1780(2) Å, β = 97.811(1)°, V = 2731.76(7) Å^3, D_X = 1.576 g cm^{-3}; μ(MoK_α) = 2.750 mm^{-1}; scan type: ϕ and ω; $2\theta_{(max)}$ = 60°; transmission factors (min; max): 0.483; 0.581; total reflections measured: 41421; symmetry independent reflections: 3990; reflections with $I > 2\sigma(I)$: 3431; reflections used in refinement: 3990; parameters refined: 179; final *R(F)* [$I > 2\sigma(I)$ reflections]: 0.0319; *wR*(F^2) (all data): 0.0820; weights: $w = [\sigma^2(F_o^2) + (0.0331P)^2 + 3.6031P]^{-1}$ where $P = (F_o^2 + 2F_c^2) / 3$; goodness of fit: 1.136; secondary extinction coefficient: 0.0012(2); final Δ_{max}/σ = 0.001; $\Delta\rho$ (max; min) = 0.46; -0.60 [e Å^{-3}].

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